Resistance to multiple antibiotics in *S aureus* is a problem that all prescribers should consider if we are to preserve our capability to treat infections. However, we need to understand that what we are trying to control is the spread of the bacteria, which are already resistant to most antibiotics, rather than the initial emergence of resistance. With that in mind, prescription must be part of a package that includes infection control and the implementation of hygiene barriers that prevent the cross infection of patients. Only then would we have any prospect to reduce resistance sufficiently to allow us to reintroduce the antibiotics we used earlier.[10] We also need to remember that antibiotic treatment for Gram positive bacteria is often less effective at controlling Gram negative bacteria. Some strains are pan-resistant and are now at least as difficult to control as MRSA, and it would be ironical if we defer one problem only to have to confront a worse one.

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Surveying the literature from animal experiments

Critical reviews may be helpful—not systematic ones

The value of animal research for finding new treatments for human diseases is a continuing debate. The starting point of the debate must be the recognition of the past contributions of animal experiments to our understanding of disease and existing treatments. We can cite the major impact of research based on animals in diseases such as polio, kidney transplantation, and Parkinson's disease. Almost every form of conventional medical treatment (including most drugs, surgical treatments, and vaccines) was developed with the help of animal research.[1–3] Most of what we know about the basic workings of the body—in humans and animals—has come to us through two centuries of animal experiments. Each decade of animal research has brought newer and deeper understanding.[4] What we lack, however, are better methods of surveying the literature on animal experiments.

Curiosity about fundamental biological mechanisms has yielded a rich harvest of useful knowledge. Although around 30% of current animal research is categorised as "fundamental" by the Home Office,[3] much of this targets specific diseases. How do we know when the information gained from animal experiments is strictly relevant for the planning of clinical trials of new drugs?

It might seem straightforward to ensure that, before a clinical trial of a new treatment commences, all relevant results from animal studies are systematically reviewed for evidence of safety and efficacy. Perhaps the best known case is that of the calcium channel blocker nimodipine as a potential neuroprotective agent after stroke. Some authors have claimed that animal experiments failed to prevent the problems that occurred in the clinical trials.[5 6] But animal experiments did reveal the deleterious effects of this drug, and these results were published. The clinical trials, however, went ahead despite evidence from animal experiments that suggested caution. Why? What are the pressures (scientific, commercial, and others) that allow trials to progress even when the evidence is not compelling or even ambiguous? And what are the requirements to weigh all available evidence in balance rather than select the data that support the personal or economic imperative? Although the example of nimodipine is well known, other powerful recent examples of animal research informing medical advance also exist—for example, the recent development of a vaccine for the severe acute respiratory syndrome.[7]

We need better methods of surveying the literature on animal experiments. The huge year on year increase in the numbers of studies reported makes it ever more likely that vital pieces of evidence go undetected. However, the proposal that systematic reviews of animal based research might solve this problem has two fundamental problems. Firstly, no mechanism exists for so called negative results to be published. Thus the absence of evidence for a particular drug action must often be inferred. This is not just an issue of publication bias; it is intrinsic to the experimental process. Scientific experiments are designed to test for evidence in favour of a particular experimental hypothesis and to abandon it if insufficient evidence is acquired.

Secondly, the style of clinical trials and of animal research have important generic differences. Clinical trials of putative treatments entail testing the treatment on a cohort of sick humans. The design can vary, but the subjects can be quite similar from one trial to

BMJ 2005;330:977–8

another, and this obviously facilitates meta-analysis and makes systematic review feasible. Pre-clinical animal trials entail testing specific effects on particular measures of physiological function while seeking to control all other possible variables. Ethical imperatives limit the number of animals used to the minimum and require that previously published studies are not simply repeated. Moreover, because of the systematic nature of the research, each experiment necessarily differs in its precise design, method, and dependent variables from those that have gone before making it much more difficult to combine data from different studies.

What we need is critical review, rather than systematic review, of all the evidence before human trials commence. A critical review compiles and evaluates the different sources of experimental evidence on a qualitative basis. A difficulty with systematic reviews is that attempts to meet precise inclusion criteria often mean useful information is excluded. The reliability and validity of each animal model needs to be assessed on its merits and its relevance to the particular clinical application. While seeking to identify and protect against major problems at the early stage of development, no model is perfect and may still miss effects that are rare or species specific, and which can be revealed only in subsequent human trials of the new treatment. Partial information, while never perfect, is better than no information.

Finally, the close association of basic and clinical science is an essential requirement for successful translation. This must include a critical appreciation of what experimental science has to offer in terms of a solution to the clinical problem.

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Childhood obstructive sleep apnoea

Serious neurobehavioural sequelae have prompted interest in diagnosis and management

Obstructive sleep apnoea is characterised by oxygen desaturation and reduced oro-nasal air flow despite preserved thoracic and abdominal respiratory effort.[1] It occurs in 1-2% of children and is more common in prematurely born infants and in black and Hispanic children.[2] As our knowledge of this condition has grown, so has concern about it among parents and clinicians. How is it best diagnosed and managed?

Habitual snoring, breathing through the mouth, periods of observed apnoea, restless sleep, urinary incontinence, inattentiveness, daytime hyperactivity, mood swings, and failure to thrive are the most common clinical manifestations of childhood obstructive sleep apnoea. How loudly a child snores is not correlated to the presence or severity of sleep disordered breathing. The most common predisposing factors are adenotonsillar hypertrophy, neuromuscular disorders, and craniofacial anomalies associated with maxillary hypoplasia, retrognathia, or macroglossia. The local release of proinflammatory cytokines such as C reactive protein, tumour necrosis factor α, and interleukin 6 might also play a part in exacerbating mucosal swelling and airway narrowing.[3]

The neuropsychological sequelae of classic childhood obstructive sleep apnoea have now been firmly established. O'Brien et al recently described 35 children with obstructive sleep apnoea (mean age 6.7 years) and 35 closely matched controls.[4] The children with sleep apnoea had notable deficits in attention span, executive function, phonological processing, visual attention, and general conceptual ability compared with the controls. The deficit in phonological processing is worrying since this serves as a basic building block in the development of reading skills.

Nocturnal polysomnographic observations in paediatric obstructive sleep apnoea were first made by Guilleminault et al in 1975.[5] Polysomnography consists of the simultaneous recording of cardiorespiratory, electromyographical, and electroencephalographic variables. The threshold of oxygen desaturation that should be used for scoring respiratory events during polysomnography remains unresolved. Federal guidelines in the United States (Medicare) stipulate a 4% oxygen drop from the baseline during respiratory events, whereas the Cleveland heart health study[2] applied a 3% desaturation threshold. These disparities are not trivial and can lead to inconsistencies from one sleep laboratory to another in diagnosing obstructive sleep apnoea. Standardisation of sleep monitoring techniques and the universal application of validated criteria for diagnosing childhood obstructive sleep apnoea remain a priority.

BMJ 2005;330:978–9